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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/691,889	10/20/2000	Yair Feld	00/20989	7655

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/691,889	FELD ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,24,28-31,33,35,43,44,49,50,55,56,59,60,68-71 and 84-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,24,28-31,33,35,43,44,49,50,55,56,59,60,68-71 and 84-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/2/06*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *6/15/06*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed October 18, 2006 has been entered. Applicant's summary of the telephonic interview of June 15, 2006 is appreciated.

The amendment filed July 6, 2006 (hereinafter referred to as "the response") has been entered. Claims 23, 24, 28-31, 33, 35, 43, 44, 49, 50, 55, 56, 59, 60, and 68-71 have been amended. Claims 32, 40, 42, 45, 46, 48, 51, 52, 54, 61-67, and 72-83 have been cancelled since the prior amendment. Claims 84-100 have been newly added.

Accordingly, Claims 23, 24, 28-31, 33, 35, 43, 44, 49, 50, 55, 56, 59, 60, 68-71 and 84-100 are pending in the instant application.

The provisional double patenting rejection is withdrawn in view of the abandonment of Application Serial No. 10/399,715.

The rejection of Claims 64-83 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the cancellation of Claim 64-67 and 72-83 and the amendments to Claim 68-71 to now recite "said implanted cells."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 24, 28-31, 33, 35, 43, 44, 49, 50, 55, 56, 59, 60, 68-71 stand rejected and Claims 84-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method of modifying the electrophysiological function of a heart of an individual and treating atrial fibrillation or ventricular tachycardia, the method comprising,

(a) providing allogeneic fibroblasts expressing an exogenous voltage-gated or inward-rectifier potassium channel polypeptide forming a functional ion channel; and

(b) implanting said allogeneic fibroblasts into the heart of the individual, such that each implanted cell of said allogeneic fibroblast forms:

(i) gap junctions with at least one cell of the heart; and

(ii) a functional ion channel,

thereby modifying the electrophysiological function of the heart and treating atrial fibrillation or ventricular tachycardia,

does not reasonably provide enablement for the full scope of the claims, where any cell type and any ion channel are used, and any disease is treated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary.

Enablement has been evaluated giving due consideration to all the Wands factors, and the following factors are particularly noteworthy:

Nature of the Invention and Scope of the Claims. The claims are directed to a method of modifying the electrophysiological function of a heart or neural tissue region of an individual, the method

comprising: (a) providing cells expressing an exogenous polypeptide forming a functional ion channel; and

(b) implanting said cells into the heart or neural tissue region, such that each implanted cell forms:

(i) gap junctions with at least one cell of the heart or neural tissue region; and

(ii) a functional ion channel;

thereby modifying the electrophysiological function of the excitable tissue region, wherein expression of said exogenous polypeptide is regulatable by an endogenous or an exogenous factor. All claims are directed to *ex vivo* gene therapy. Various claims recite that the method is utilized for regulating cardiac arrhythmia. Various claims (e.g., Claims 35, 84, and 90) recite that the method is utilized for treating Parkinson's disease. The specification asserts that the present invention (*i.e.*, the method of *ex vivo* gene therapy) can be used for restoring normal electrophysiological function to damaged tissues such as heart, nerve, or glandular tissues (page 9, lines 4-7). Thus, the nature of the invention relates to treatment of patients having a variety of deficits in excitable tissues. The claims are broad in scope, encompassing treatment of a variety of diseases and disorders, including Parkinson's disease and cardiac arrhythmias. Thus, the claimed method encompasses treatment of a wide variety of disorders. The specification does not assert any use, other than treatment, for the claimed method of *ex vivo* gene therapy.

The specification contemplates that the method of the invention can be applied to treat a variety of cardiac arrhythmias (page 58, lines 17-18). The specification further contemplates that astrocytes transfected with selected ion channels may be used to modulate focal pathological areas in the central nervous system (CNS), thus enabling treatment of disorders such as epilepsy, Parkinson and the like (page 59, lines 18-21). Thus, the claims encompass treatment of a huge variety of diseases of the CNS. Furthermore, the claims are very broad in scope with regard to the type of therapeutic effect to be achieved by the method (e.g., regulating neuronal discharge, regulating cardiac arrhythmia, rhythm

control for atrial fibrillation). All claims are presently drawn to *ex vivo* gene therapy, wherein the implanted cell is transformed prior to transplantation. Moreover, the claimed method covers the use of any cell type and any ion channel or transporter.

The only utility asserted in the specification for the claimed method is to produce a therapeutic effect. Thus, the claims are directed to *ex vivo* gene therapy methods of considerable breadth.

Amount of direction or guidance presented and the presence or absence of working examples. The teachings of the specification are limited to analysis of conduction properties of cells in cultures in a variety of assays (Example 5, pages 50-59). In Example 5, the electrical properties of fibroblasts transfected with the Kv1.3 channel coding sequence (Kv1.3 fibroblasts) in co-cultures with unmodified rat ventricular cardiomyocytes were analyzed. The presence of Kv1.3 fibroblasts in co-culture with cardiomyocytes caused a variety of changes in the electrophysiological function of cardiomyocyte monolayer cultures. The specification does not provide any working examples with regard to treatment of a diseased animal by implantation of cells as recited in the claims. The Declaration of Dr. Feld, filed March 3, 2003, describes experiments where a rat fibroblast cell expressing an exogenous polypeptide Kv1.3 ion channel is implanted into the rat heart (left ventricular free wall or atrio-ventricular junction). The promoter used to drive expression of the Kv1.3 ion channel is not disclosed. The effective refractory period was determined prior to transplantation and 5-7 days following transplantation. The average refractory period of the hearts prior to transplantation was 104 ms and 166 ms following transplantation with Kv1.3 fibroblasts. Application of margatoxin, a specific Kv1.3 channel blocker, caused the refractory period to decrease to 130 ms in the transfected group, while no change was seen in the non-transfected group. Thus, it was concluded that the electrophysiological modulation of the cardiac tissue was mediated by Kv1.3. The animals used in the experiments were healthy animals and therefore no treatment effect was noted.

With regard to *ex vivo* gene therapy the specification provides only limited and general guidance for the treatment of a few diseases, including epilepsy, diabetes, and cardiac arrhythmias. The specification fails to provide any **specific guidance** on the generation of the nucleic acid construct to be used in the gene therapy method for the treatment of any specific disease or disorder. Only general guidance is provided.

State of the prior art and predictability of the art. At the time of the invention, successful implementation of *ex vivo* gene therapy protocols was not routinely achievable by those skilled in the art. This is reflected in numerous references. With particular regard to the treatment of cardiac arrhythmias, Donahue et al. (2005a) reports that "[t]he investigation of gene therapeutic strategies to treat cardiac arrhythmias is in its infancy" (page 221, column 1, paragraph 2) and "[a]rrhythmia gene therapy is a field in its infancy, and future human applications are dependent on solutions to the problems discussed in this review" (abstract). The authors also note several examples of cardiac arrhythmia ion channel gene therapy experiments in animal models and state that "[i]t should be noted for all these examples, and indeed for the field as a whole, that the pathophysiology of arrhythmias is extremely complex" (page 222, column 1, paragraph 2) and "[w]hen dealing with situations of this complexity, surprises will undoubtedly occur as the cardiac system adapts to the therapeutic intervention" (page 222, column 1, paragraph 2). The authors also point out that "[c]urrent problems in the field of gene therapy include ... the inability to control the duration and level of gene expression" (page 222, column 3, paragraph 1). Thus, it is evident that, given the instantly claimed method, success of the protocol is critically dependent on matching a given disease with an appropriate therapeutic construct and an appropriate cell type. The appropriate therapeutic construct must be made by judicious selection of an appropriate promoter, along with other genetic control elements, and an appropriate ion channel gene (or transporter) to effect the desired therapy in the tissue of interest. The construct must then be transfected into an appropriate cell type, such that the particular combination of the various parameters leads to the desired therapeutic result. Although

considerable experimental data is available on the function of various ion channels, particularly in neurons, reports suggest that "several tens of different ion channel types are present at the surface membrane and inside the presynaptic nerve terminal" (Meir et al., page 1020, column 1, paragraph 2) and that "[t]he number of different ion channel molecules is probably well over a hundred" (Meir et al., page 1020, column 1, paragraph 2). Given the very broad scope of the claims, development of a therapeutic protocol within the scope of the claims would require undue experimentation.

The instant specification fails to provide sufficient guidance to the skilled artisan to produce a treatment effect across the full scope of the claims, or even for particular embodiments contemplated in the specification. Numerous factors complicate the gene delivery art which cannot be overcome by routine experimentation. These include the *in vivo* consequences of altered gene expression and protein function, the level of mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. In the instant application, the specification provides little specific guidance with regard to the generation of a nucleic acid construct to be used in an *ex vivo* gene therapy method for the various diseases to be treated. In the absence of specific guidance, the skilled artisan would have been required to develop successful protocols for practicing the claimed methods over a very large and improbable scope, without guidance on a starting point or the direction in which experimentation should proceed. However, given that the *ex vivo* gene therapy art was considered highly unpredictable, the skilled artisan would have been required to engage in undue experimentation to come up with successful gene therapy protocols. Even in the field of cardiac arrhythmias, despite intensive effort on the research front, the existence of successful gene therapy treatment protocols was extremely limited in 2000.

Tomaselli et al. (2003) report that:

> "Direct and indirect gene transfer is an important tool in the study of normal and pathologic cardiac electrophysiology. The use of gene transfer in clinical therapeutics remains intellectually appealing but is subject to a number of substantial challenges before implementation in humans can be considered. These challenges are relevant to

> gene therapy generically and to the treatment of cardiac arrhythmias specifically." (page 549, column 2, paragraph 2).
>
> and further that:
>
> "Problems that are more specific to gene therapy for cardiac arrhythmias are exemplified by, but not limited to, our lack of understanding of the molecular mechanisms of many arrhythmias and the spatial complexity of expression of ion channels, which curbs the utility of transfer of a single ion channel species." (page 549, column 2, paragraph 4).

Although *ex vivo* gene therapy approaches to improve automaticity are being developed, Donahue et al. (2005b) reports that "[o]verall, gene transfer approaches to increase cardiac automaticity are in early stages of development" (page 159, paragraph 4) and that "[o]ngoing work in this field has the potential for tremendous impact if the correct gene or combination of genes is identified to allow recreation of true pacemaker activity" (page 159, paragraph 4).

In an article published well after the filing date of the instant application, Rubanyi (2001) teaches that the problems described above remain unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far ..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene expression control systems (see especially the section under "3. Technical hurdles to be overcome in the future", pages 116-125).

Beyond the technical barriers to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claimed methods encompass the use of a wide variety of genetic constructs to treat a wide variety of diseases. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic (p. 131, paragraph 4). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among

multigenic diseases" (p. 113, paragraph 4). As of the filing date of the instant application however, even the most promising areas presented barriers to successful gene therapy that could not be overcome by routine experimentation. Rather, the prior art shows that intensive investigation has met with limited success.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

Given the unpredictability in the *ex vivo* gene therapy art, and further given that the specification fails to provide specific guidance on which nucleic acids encoding which protein can be used to treat a specific disease of interest, across the very broad scope, the skilled artisan would have been required to engage in undue experimentation to develop a method within the scope of the claims for treating any particular disease.

Given the limited examples, the limited guidance provided in the specification, the limited showing of therapeutic benefit upon application of the claimed method, the very broad scope of the claims, and the unpredictability for producing a therapeutic effect upon implantation of a genetically modified cell, undue experimentation would have been required for one skilled in the art to develop a

protocol within the scope of the claims for treating a wide variety of diseases, and moreover to develop protocols across the full scope.

The Declaration of Dr. Feld, filed July 6, 2006, has been fully considered and is found to be partially persuasive. Applicants' response and the Declaration of Dr. Feld are generally persuasive with regard to the use of allogeneic fibroblasts genetically modified to overexpress an exogenous Kv1.3 polypeptide forming a functional ion channel, wherein the implanted cell forms a functional ion channel and gap junctions with cells of the heart. However, the response is not persuasive with regard to the implantation of other cell types or cells that express other ion channels. Further, the Declaration is not persuasive with regard to the use of the method to treat Parkinson's disease.

At pages 11-12 of the response, Applicants point to the studies described in the Declaration and studies of the post-filing art of Potapova et al. (2004). Applicants argue that the results provide ample support for the treatment of a variety of cardiac indications using a number of cells, ion channels and construct systems in well-known animal models. Applicants assert that these results support the scope of the claimed invention. As regards cardiac indications, the Declaration describes *in vivo* transplant studies in pigs where genetically modified fibroblasts were transplanted to the heart in either the ventricular wall or AV node by direct injection or catheterization, respectively. Both wild-type and a mutant form of the Kv1.3 channel (Kv1.3 H401W) and the wild-type Kir2.1 channel were used in the studies. The expression of each was driven by a CMV promoter. The results showed that the ventricular effective refractory period (ERP) was extended with fibroblasts overexpressing the wild-type Kir2.1, as well as with those overexpressing Kv1.3 H401W. For AV node modification, only fibroblasts overexpressing the mutant Kv1.3 H401W channel were transplanted. The results showed that the effective refractory period was extended. Thus, the studies described in the Declaration provide support for the use of allogeneic fibroblasts overexpressing a voltage-gated or inward-rectifier potassium channel to treat ventricular tachycardia or atrial fibrillation. Applicants further assert that the results described by Potapova et al.

(2004) for studies involving the transplantation of mesenchymal stem cells overexpressing the indiscriminate ion channel HCN2. The cells were transplanted into the ventricle of canine heart and exhibited pacemaker function when bradycardia was induced in the heart. However, the instant specification does not provide specific guidance for using mesenchymal stem cells in the claimed invention and the reference of Potapova et al. (2004) is post-filing art. Thus, one of skill in the art would not have had the benefit of the teachings specific to the use of mesenchymal stem cells overexpressing an indiscriminate ion channel at the time of the instant invention. Claims limited to the use of allogeneic fibroblasts overexpressing a voltage-gated or inward-rectifier potassium channel are therefore appropriate, given the unpredictability in the art and the limited guidance of the specification.

At pages 12-13 of the response, Applicants point to the studies described in the Declaration pertaining to the use of fibroblasts overexpressing Kv1.3 to improve the aymmetric rotational behavior of 6-OHDA-lesioned rats. Applicants assert that these results support the use of cells expressing potassium channels for the treatment of Parkinson's disease. However, the experiments described in the Declaration used fibroblasts that overexpress a potassium channel in combination with the gap junction protein connexin36 (Cx36). This enables the fibroblasts to form gap junctions with neurons expressing Cx36. However, the instant claims do not require the expression of the gap junction protein and the Declaration makes it clear that it is an essential element. Furthermore, the instant specification does not provide specific guidance for transplanting Cx36-expressing fibroblasts into the globus pallidum to modify the GABAergic inhibitory system. Thus, the Declaration does not convincingly showed that experiments conducted in accordance with the teachings of the specification were successful in treating Parkinson's disease.

At page 13 of the response, Applicants assert that various promoters could be used to drive the expression of the ion channel. Applicants point to the general guidance of the specification teaching constructs containing inducible and constitutive promoters and argue that the skilled artisan would have

been able to readily select the optimal promoter sequence using the *in vitro* and *in vivo* assays described in the specification, without resorting to undue experimentation. These arguments are generally persuasive and the scope of enablement indicated is therefore not limited to the use of any particular promoter. However, neither the specification nor the Declaration demonstrate that cells comprising constructs that use inducible promoters would integrate and electrically couple appropriately upon transplantation in the absence of expression of the ion channel, which then may be later induced. Thus, claims explicitly reciting inducibility would not be considered enabled, given the unpredictability in the art and the limited guidance of the specification.

At page 14 of the response, Applicants point to a variety of gene therapy publications and argue that gene therapy is not unpredictable because a few successes have been reported. However, while many investigators recognize and praise the potential of gene therapy, a "potential" is not sufficient to enable the claimed invention as it relates to *in vivo* gene therapy, as it is well established that the invention must be enabled at the time of filing. A potential for the future of gene therapy does not constitute enablement, but rather is suggestive of a technology that is still undeveloped. One of skill in the art would conclude that the development of gene therapy protocols is not routine if potential successes lie predominantly in the future, not in the past. The references cited in Applicants' response and by the Examiner provide clear evidence that **intensive effort** has been applied to the development of gene therapy protocols with minimal success. None of the gene therapy methods that Applicants point to were developed using routine experimentation. In fact, the studies cited relating to successful clinical trials (Tuszynski et al., 2005) in gene therapy were considered breakthroughs in the field. Furthermore, if it was a simple matter to take the vectors used by others and, with routine experimentation, manipulate them and apply them in techniques for the treatment of other diseases, many successful gene therapy protocols would already exist. However, this is not the case, as evidenced by the references cited by the Examiner. Further **research** is required to accomplish these goals, not routine experimentation. Thus, the references cited by

Applicants do not constitute evidence that only routine experimentation is required for the development of gene therapy protocols. On the contrary, the references clearly indicate that, in each instance, **intensive investigation** was required to develop experimental protocols. In an unpredictable art, considerable specific guidance is needed from the specification. In the instant case, given the unpredictability in the field of gene therapy, the limited guidance in the specification with regard to the design and implementation of vectors for gene therapy, the lack of applicable working examples directed to administering polypeptide-encoding nucleic acids to achieve improved function within excitable tissues, and the broad scope of the claims with regard to the type of cells and vectors to be used, and the type of polypeptide-encoding nucleic acid to be used, undue experimentation would have been required for one skilled in the art to practice the claimed method over the full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23, 28-31, 43, 44, 49, 50, 68, 69, 70, 88, and 89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 is indefinite in its recitation of "such that each implanted cell forms of said cells" because the phraseology is grammatically incorrect and it is unclear what is meant. It appears that the amendment may have been intended to read "such that each implanted cell <u>of said cells</u> forms" as was done for Claims 28, 29, 33, and 35. Claims 31 and 68 are indefinite insofar as they depend from Claim 23.

Claims 28, 29, and 87 are indefinite in their recitation of "an activity of said transporter" because "said transporter" lacks antecedent basis. Claims 30, 43, 44, 49, 50, 69, 70, 88, and 89 are indefinite insofar as they depend from Claims 28, 29, and 87.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history

information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER